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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/734,936	12/12/2003	Wonchul Suh	CL1878USNA	2510

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EXAMINER	
MCGILLEM, LAURA L	
ART UNIT	PAPER NUMBER
1636	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	02/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/734,936	SUH, WONCHUL	
	Examiner	Art Unit	
	Laura McGillem	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/17/2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-11,13-24 and 26-30* is/are pending in the application.

4a) Of the above claim(s) *2 and 18-19* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,7-11,13-17,20-22 and 26-29* is/are rejected.

7)☒ Claim(s) *5,6,23,24 and 30* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *12 December 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

It is noted that claims 1, 3, 9, 17, 21-23, and 28 have been amended in the response filed 11/17/2006. Claims 2 and 18-19 are withdrawn and claims 12 and 25 are cancelled. Claims 1, 3-11, 13-17, 20-24 and 26-30 are under examination.

Claim Objections

Claim 28 had been amended to remove dependency from withdrawn claims. The objection to claim 28 has been withdrawn.

Claim Rejections - 35 USC § 112

It is noted that the Office Action mailed 5/25/2006 on page 3 does reject claim 20 for indefiniteness because of the phase "said promoter", however this phrase appears in claim 21 and 22 not in claim 20. Claim 20 was inadvertently listed instead of claims 21-22. However, claim 20 was properly rejected insofar as it is dependent on indefinite claim 17. Claims 1, 3, 9, 17, 21-23, and 28 have been amended and therefore the rejection of claims 1, 3-11, 13-17, 20-24 and 26-30 under 35 U.S.C. 112, second paragraph has been withdrawn.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 3, 7-11, 15-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perkins et al (Application Publication No. 2002/0151058, of record) in view of Yu et al (of record) and further in view of Prideaux et al (U.S. Patent No. 6,472,183).

This rejection is being maintained for reasons of record in the previous Office Action (mailed 5/25/2006) and for reasons outlined below.

Applicants submit that the Office Action dated December 20, 2005 states on page 9, that Perkins is the closest prior art, and further records,

"'Perkins and Tugendreich do not teach the use of the λ Red recombination system, recombination into the bacterial chromosome or a second recombination reaction to eliminate the selectable marker."

Applicants submit that the three individual elements may have existed individually before the date of filing, however, similar to the present invention that is a combination of three known types of nucleic acid molecules into a succinct and elegant system, the invention itself is a non-obvious and novel combination of three elements of art into a new invention. Even if Perkins et al, Yu et al and Prideaux et al contain all the elements of the present invention (although the Applicant protests that they do), one of ordinary skill in the art would not have the motivation to combine Perkins et al, Yu et al and Prideaux et al to create the present invention.

Applicants submit that the Office Action (5/28/2006) suggests on page 6 that one skilled in the art would be motivated to combine Perkins et al and Yu et al "because, Yu et al teach that it is difficult to recombine linear DNA into *E. coli* genomes and that this

system is an improvement over the art at the time when the invention was made." Applicants submit that the triple recombination system of Perkins et al in Fig. 3 as cited in the Office Action is not linear DNA, but rather a circular vector. Applicants submit that such vectors are well known for stably transforming bacteria, especially *E. coli*. The problem cited by Yu et al is the normal exonuclease activity that degrades linear DNA is not a problem for the artisan practicing Perkins et al with a circular plasmid vector. Therefore one skilled in the art practicing Perkins et al would not have the problem suggested by Yu et al nor would the artisan recognize Yu et al as a potential part of a new method because Yu et al discusses linear fragments and Perkins is directed to circular stable vectors.

Applicants submit that the Office Action (5/28/2006 page 8) suggests that,

"it would have been obvious to one of ordinary skill in the art to modify the methods of Perkins et al to include a selectable marker flanked by recombination sequences so that the selectable marker could be excised from the host chromosomes after homologous recombination because Perkins et al teach a method of introducing DNA sequences into bacterial genome for production of genes of interest using selectable markers to screen for the presence of the introduced vector and Prideaux et al teach that genes for antibiotic resistance used for the selection can be undesirable after selection has taken place."

Applicants submit that this reasoning is flawed when the selectable marker is considered in the context of the Perkins et al system. Applicants submit that Perkins et al taken alone teaches the uses of a plasmid vector with a selectable marker. The selectable marker has a two-fold function, first it is used to identify transfected bacteria that contain the gene of interest for isolation. Second it is used to maintain the plasmid in the isolated bacteria population for the production of the gene of interest. Applicants submit that it is well known to one of ordinary skill that a plasmid can be lost if the

growth of the bacteria culture is not continually selected for a trait contained within the plasmid. Applicants submit that therefore one skilled in the art practicing Perkins et al would not be motivated to combine with Prideaux et al to introduce flanking recombination sequences because the skilled artisan would desire to retain the selectable marker to properly practice Perkins et al. Applicants submit that the selectable marker is crucial to the practice of Perkins et al as disclosed and therefore one skilled in the would want to increase the selection for the marker and not be motivated to eliminate said marker as described in Prideaux et al.

Applicants submit that one skilled in the art practicing Perkins et al with a stable transfected gene of interest on a circular plasmid would not be motivated to adopt a system for chromosomal integration designed for linear fragments. Applicants submit that it said skilled artisan does not have need for chromosomal integration. Without first incorporating the gene of interest into the chromosome, combining Prideaux et al and Perkins together would be a fatal combination. Applicants submit that using a second recombinase reaction to eliminate the selectable marker as suggested by Prideaux et al destroys the stability of the vector as transfected by the Perkins et al system. It would take an inventive step such as described in the instant application to use a triple homologous recombination event, combined with the λRed system for bacterial chromosome integration, and incorporating a flanking recombination sequence so that after chromosomal integration has been achieved and stably ensured, the selectable marker can be removed. Applicants submit that one skilled in the art practicing Perkins

et al would not be motivated to construct a removable necessary component of the Perkins et al system, that is the selectable marker, by a second recombinase reaction.

Applicants submit that one of ordinary skill would not be motivated by Yu et al to combine chromosome incorporation into the already stable and effective practice of Perkins et al, especially considering that Yu et al is directed to the problems of a linear fragment and the artisan has a circular stable plasmid that is not subject to the problem that Yu et al solves.

Applicant's arguments filed 11/17/2006 have been fully considered but they are not persuasive.

Applicant appears to present three main arguments:

1. There is no motivation to combine Yu et al and Perkins et al because Yu et al addresses recombining linear DNA, Perkins et al teach circular DNA, and that the skilled artisan would not recognize the teachings of Yu et al as a new aspect of the method.

Although Applicants submit that the triple recombination system of Perkins et al in Fig. 3 is not linear DNA, but rather a circular vector, Perkins et al does teach the use of some linear nucleic acid sequences in the method. For example, Figure 3 illustrates linear fragments 301 and 302. Perkins et al discloses linear expression vector intermediates (see paragraph 0010, 0023, in particular). Perkins et al also discloses method using either circular or linearized vectors (see paragraph 0034, for example). These linear elements are recombined into a vector and then in some embodiments become circular, as part of the recombination method. Perkins et al exemplifies an

embodiment of this method performed in yeast. Yu et al teach that "Unlike yeast, *E.coli* is not readily transformed by linear DNA fragments due in part to the rapid degradation of the DNA" by exonucleases (see page 5978). In order to perform the method of Perkins et al in *E coli* and not yeast, the skilled artisan would need to address the problem of native exonucleases in *E. coli* at whatever stage that the linear elements are being employed in the method. Therefore the skilled artisan practicing Perkins would be motivated to modify the method of Perkins et al and include the recombination system as taught by Yu et al. As stated in the previous Office Action, the motivation to use the λ Red recombination system is the expected benefit as exemplified by Yu et al of being able to recombine PCR-generated linear DNA constructs comprising very short regions of homology into the *E.coli* genome instead of a yeast genome in an efficient manner without additional steps that had been required using methods previously used in the art.

2. The motivation to include the removable selectable marker of Prideaux et al in the method of Perkins et al is flawed because one practicing the method of Perkins et al would want to retain the selectable marker.

Perkins et al teach in paragraph 0011 that a selectable marker is useful for screening a transformed cell either by the presence of the marker or in one embodiment by the absence of a negative marker (a marker deleterious to the cells that is excised during homologous recombination). Perkins et al provide a specific definition of "selectable marker" as they intend (see paragraph 0025). Perkins et al does not specifically teach retention of the selectable marker to properly practice the disclosed

method. Further, Perkins et al do not exclude a step of excising the selectable marker and in the case of negative selectable markers, do contemplate their removal during recombination.

Although there would be some situations in which the skilled artisan might want to retain a selectable marker in a transformed cells as suggested in the Applicants arguments, Prideaux et al provide motivation for removal of a selectable marker by recombination in situations in which the retention of a selectable marker is undesirable after homologous recombination with the host chromosome. Furthermore, in an obviousness rejection a rationale different from Applicant's is permissible.

The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant. >See, e.g., *In re Kahn*, 441 F.3d 977, 987, 78 USPQ2d 1329, 1336 (Fed. Cir. 2006) (motivation question arises in the context of the general problem confronting the inventor rather than the specific problem solved by the invention); *Cross Med. Prods., Inc. v. Medtronic Sofamor Danek, Inc.*, 424 F.3d 1293, 1323, 76 USPQ2d 1662, 1685 (Fed. Cir. 2005) ("One of ordinary skill in the art need not see the identical problem addressed in a prior art reference to be motivated to apply its teachings.");< *In re Linter*, 458 F.2d 1013, 173 USPQ 560 (CCPA 1972) (discussed below); In re Dillon, 919 F.2d 688, 16 USPQ2d 1897 (Fed. Cir. 1990), cert. denied, 500 U.S. 904(1991) (discussed below). Although *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (Bd. Pat. App. & Inter. 1993) states that obviousness cannot be established by combining references "without also providing evidence of the motivating force which would impel one skilled in the art to do what the patent applicant has done" (emphasis added), reading the quotation in context it is clear that while there must be motivation to make the claimed invention, there is no requirement that the prior art provide the same reason as the applicant to make the claimed invention. M.P.E.P. 2144 [R-5]

3. There is no motivation to incorporate Yu et al to combine chromosome incorporation into the already stable and effective practice of Perkins, especially

considering that Yu et al teach a linear fragment and the artisan has a circular stable plasmid that is not subject to the problem that Yu et al solves.

Applicants suggest that combining Prideaux et al and Perkins et al together without first incorporating the gene of interest into the chromosome would be a fatal combination, however, the combination of the teachings of Prideaux et al and Perkins et al alone without Yu et al is not being used in this rejection. Applicants submit that the skilled artisan practicing Perkins et al would not be motivated to add a removable necessary component (i.e. the selectable marker by a second recombinase reaction). As discussed above, vector stability is not a mandate of the method taught by Perkins et al, only that a selectable marker be present in order to screen those cells that have been transformed.

Applicants submit that one skilled in the art practicing Perkins et al with a stable transfected gene of interest on a circular plasmid would not be motivated to adopt a system for chromosomal integration designed for linear fragments and would not be motivated by Yu et al to combine chromosome incorporation into the already stable and effective practice of Perkins et al, especially considering that Yu et al is directed to the problems of a linear fragment and the artisan has a circular stable plasmid that is not subject to the problem that Yu et al solves.

While Perkins et al do not teach chromosomal integration, Perkins et al do teach methods of triple homologous recombination for production of vectors and exemplify their use in yeast cells. Yu et al disclose an efficient recombination system (λRed recombination) for use chromosomal engineering and also disclose a problem that

directly relates to the teaching of Perkins et al, specifically that unlike yeast, *E.coli* is not readily transformed by linear DNA fragments because of exonuclease degradation. The teachings of Perkins et al contemplate and make use of linear DNA fragments in methods to transform cells. In order to use the method of Perkins et al in cells other than yeast, the problem of exonuclease degradation can be addressed by using the method of Yu et al including chromosomal engineering using λRed recombination in cases wherein chromosomal integration is desirable as in Yu et al. Therefore, the skilled artisan would be motivated to combine the teaching of these three references and render the claimed methods obvious or lacking an inventive step.

Claims 1, 3-4, 7-8, 11, 13-17, 20-22 and 26-29 are rejected under 35 U.S.C. 103(a) as being unpatentable over Perkins et al (of record) in view of Yu et al (of record) and further in view of Welch et al (Application Pub. No. 2002/0187544) as evidenced by Guzman, et al (J. Bacteriol., 1995, 177(14): 4121-4130).

This rejection is being maintained for reasons of record in the previous Office Action (mailed 5/25/2006) and for reasons outlined below.

Applicants submit that even if Perkins et al, Yu, Welch et al and Guzman et al contain all the elements of the present invention (although the Applicant protests that they do), there is not sufficient motivation to combine. Applicants submit that Yu et al is directed to the stability problem of linear DNA fragments, whereas Perkins utilizes a circular vector that is not degraded by exonuclease activity.

The Office Action (5/28/2006, page 13) states that it would have been obvious to one practicing Perkins et al to incorporate Welch's "excisable selectable marker system because Perkins et al teaches the methods of introducing promoters and genes of interest into a bacterial chromosome". Applicants submit that this contradicts the statement on page 9 of the December 20, 2006 Office Action, "Perkins and Tugendreich do not teach ... recombination into the bacterial chromosome..." (Full quote above). Applicants submit that the fact is that Perkins et al do not teach nor require bacterial chromosome integration. Perkins et al conveys stability of transfection by use of a selectable marker on a circular plasmid. Applicants submit that the skilled artisan would be aware of the importance of the selectable marker to the stability of the plasmid in the bacteria population and would take steps to maintain said marker, not to eliminate it. Perkins et al effectively teaches away from excising the selectable marker. There is no motivation to combine Perkins et al with Welch et al or Guzman et al, neither is motivation to combine Perkins et al with Yu et al.

Applicant's arguments filed 11/17/2006 have been fully considered but they are not persuasive. Applicant appears to present three main arguments.

The previous Office action does state on page 13 that Perkins et al teaches the methods of introducing promoters and genes of interest into a bacterial chromosome, this is clearly an inadvertent failure to add the phrase "combined with Yu et al" to the sentence. The combination of Perkins et al and Yu et al is extensively discussed in the previous rejection and the title of the Yu et al paper "An efficient recombination system for chromosomal engineering in *Escherichia coli*" reflects its content related to bacterial

chromosome integration. The motivation to combine Perkins et al with Yu et al regarding the stability of linear DNA fragments is detailed above and also applies to this rejection. Although Applicants submit that Perkins et al effectively teach away from excising the selectable marker, absent evidence to the contrary, Perkins et al does not exclude excision of the selectable marker, but teach that it would be used to screen transformants. Perkins et al do contemplate an embodiment in which negative markers are excised (see end of paragraph 0011).

Applicants submit that there is no motivation to combine Perkins et al with Welch et al evidenced by Guzman et al. Applicants do not submit further arguments against the combination of Perkins et al, Yu et al, Welch et al or Guzman et al. As discussed in the Office Action mailed 5/25/2006, it would have been obvious to one of ordinary skill in the art to further modify the methods of Perkins et al and Yu et al to incorporate the teachings of Welch et al because Welch teaches that expression of the gene of interest can be examined with a promoter (foreign promoter) independently of the native promoter, which is dependent on D-serine. The motivation to do so is the expected benefit of being able to accurately examine a variety of phenotypes created by various deletions and mutations independently from D-serine induced expression (i.e. any induced signaling necessary for activation of the native promoter) (see paragraph 0065, in particular). Therefore the claimed methods are made obvious by Perkins et al, in view of Yu et al and further in view of Welch et al as evidenced by Guzman et al.

Conclusion

Claims 1, 3-4, 7-11, 13-17, 20-22 and 26-29 are rejected. Claims 5-6, 23-24 and 30 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laura McGillem whose telephone number is (571) 272-8783. The examiner can normally be reached on M-F 8:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Laura McGillem, PhD
2/16/2007

CELINE QIAN, PH.D.
PRIMARY EXAMINER